APPENDIX F: Office Action of October 12, 2000

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Wim

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/674,311	07/01/96	OLOPADE	ARSB:509--1

EXAMINER	
ART UNIT	PAPER NUMBER
1655	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Action Required: X-ferred
Date Due/Done: 2-8-00
By: FtJ Checked BB

RECEIVED
Date(s) Docketed: 1-12-01 Response to Office Action Date; 4-12-01 Final Deadline
OCT 25 2000
Client: ARSB:509--1
Attorney(s): WIM
Initials: chc

Office Action Summary

Application No.	Applicant(s)
08/674,311	Olopade et al
Examiner	**Group Art Unit**
Lisa Athur	1655

☒ Responsive to communication(s) filed on *Jul 12, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *39-96* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *39-96* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This action is in response to the paper filed July 12, 2000. Currently claims 39-96 are pending. All of the arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. Any rejections which have not been reiterated have been withdrawn. This action is contains new grounds of rejection and is therefore not final.

MAINTAINED REJECTIONS

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39-50,52-57,59, 60, 67-76,78,80-83,88-94 are rejected under 35 U.S.C. 102(b) as being anticipated by Kamb et al. (1994).

Kamb et al. teach isolated polynucleotides containing the tumor suppressor gene MTS1 which maps to 9p21-22. The cosmid that contains MTS1 of Kamb et al also contains the human methylthioadenosine phosphylase gene (MTAP) since these two genes are tightly linked. Thus the cosmid of Kamb et al is an isolated polynucleotide comprising the sequence of SEQ ID no 1 which is a sequence region that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO 2. Necessarily then, the polynucleotide of Kamb et al. Comprises at least 21, 30, 40 or all contiguous bases from nucleotides 122-970 of SEQ ID NO 1 (limitations of claims 40-43). Since the polynucleotide of Kamb et al. Encodes the MTAP gene, it inherently meets the limitations of claims 45 and 46 that the encoded polypeptide promotes melanoma senescence and

suppresses glioma cell tumor generation. The cosmid used in Kamb et al. was at least 849 base pairs in length since it contains the CDKN2 which is target than 849 base pairs (limitations of 47-49). Kamb et al teaches a method for detecting a nucleic acid comprising a sequence encoding MTAP by hybridization with a probe comprising at least 21 bases of SEQ ID NO 1 because Kamb et al. Teaches a Southern blot (Figure 2) was performed using human genomic DNA and a probe which was a cosmid which contains the MTAP gene. Therefore, a nucleic acid containing the MTAP would be detected by hybridization of the cosmid of Kamb et al since the same probe was used by Kamb et al. that was used in the claimed method (claims 78-83).

Response to Arguments

The response traverses the rejection on the following grounds. The response argues that Kamb et al. only sequenced parts of cosmid C5 to identify the MTS1 and MTS2 genes and did not sequence SEQ ID NO 1. The response states that Kamb et al. Did not identify, isolate or sequence a polynucleotide comprising a nucleic acid sequence from SEQ ID NO 1. The response further states that even if MTAP is comprised on cosmid C5, Kamb et al. Did not disclose a polynucleotide compromising the sequence from SEQ ID NO. 1. The response states that conception of a gene requires isolation of the gene. The response states that prior to the disclosure of SEQ ID NO 1 there was no understanding of where the sequence encoding MTAP was located.

All of these arguments have been thoroughly reviewed but are deemed non-persuasive for the following reasons. The claims are drawn to an isolated polynucleotide comprising a sequence

region that encodes a polypeptide comprising the amino acids sequence of SEQ ID NO 2 or comprising fragments of SEQ ID NO 1. Because of the way the claims are written, the claims encompass any isolated polynucleotide of any size which contains somewhere within its sequence a region that encodes SEQ ID NO 2 or contains the recited fragments of SEQ ID NO 1. The claims are not limited to a polynucleotide which encodes only SEQ ID NO 2 or which contains only the recited fragments of SEQ ID NO 1. As written the recited sequences can be embedded within much large isolated polynucleotides such as the isolated cosmid C5 polynucleotide. There is no argument that Kamb et al. Does not teach an isolated polynucleotide consisting of only the MTAP coding sequence but the none of the rejected claims are limited to such an embodiment. Determining the nucleotide sequence of a known polynucleotide does not distinguish the polynucleotide from that of the prior art because the nucleotide sequence is an inherent characteristic of any polynucleotide. Because Kamb et al. Teach a large isolated polynucleotide which contains somewhere within its structure the nucleic acid sequence encoding the MTAP polypeptide, Kamb et al. have in fact taught the isolation of a polynucleotide containing SEQ ID NO 1 and consequently, have "conceived" of the claimed polynucleotide even though Kamb et al. Certainly has not defined the specific position of MTAP or a polynucleotide consisting of SEQ ID NO 1 or fragments of SEQ ID NO 1. Therefore, this rejection is maintained.

Claims, 54-66, 74-76, 78-83, 88-94 are rejected under 35 U.S.C. 102(b) as being anticipated by Nobori et al.

Nobori et al. teach that a methylthioadenosine phosphylase cDNA was isolated and used to probe a human lambda-phage cDNA library and a 2000 base pair fragment was found to contain the 3' end of the MTAP gene (page 753, col. 2, paragraph 3). This sequence was used as a probe for chromosome walking, I .e. in a hybridization detection reaction. The MTAP HinDIII fragment was inserted into a vector and transformed into a host cell page 754). It is noted that Nobori et al. Only discloses a 3' fragment of the human MTAP gene. However, the claims as written read on polynucleotides containing fragments of the MTAP gene as small as 10 bases.

Response to Arguments

The response traverses the rejection on the following grounds. The response argues that since physical map of the cDNA containing the 3' end of the MTAP gene shown in the Nobori et al. (1994) references is incorrect, the ordinary artisan would have been lead to look in the wrong place for a polynucleotide comprising SEQ ID NO 1. The response also argues that Nobori et al. Only teach a small fragment of the MTAP gene and did not teach the sequence of this fragment. The response argues that Norbori et al. did not characterize, isolate or sequence a polynucleotide comprising SEQ ID NO 1 and that the aim of their paper was to study a completely different gene.

Again the response cites *Amgen Inc v. Chugai Pharmaceutical Co., Ltd.* as evidence that Nobori et al. Did not teach a polynucleotide comprising SEQ ID NO 1 because they do not teach the isolation of sequencing of this nucleic acid and do not mention kits or methods of using the polynucleotide.

All of the arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. Claims 39-42,45-53 have been withdrawn from this rejection because the claims are limited to polynucleotides which must at least contain a nucleic acid which encodes a complete SEQ ID NO 2. Since Nobori et al. only teach a fragment containing the 3' end of the MTAP gene, Nobori et al. Does not read on these claims. However, claims 54-66 are broadly drawn to a nucleic acid of from 850-10,000 bp comprising a gene encoding a MTAP polypeptide which polypeptide comprises a region of 10, 20, or 30 amino acids from SEQ ID NO. 2. Since Nobori et al. Teach a 2000 base pair nucleic acid containing the 3' end of the MTAP gene which encodes the COOH end of the MTAP polypeptide, Norbori et al. Teach nucleic acids which meet all the limitations of the claims. The fact that Nobori et al. Do not teach the nucleotide sequence of the 3' end of the MTAP gene does not obviate the fact that they were in possession of a nucleic acid which encodes an MTAP polypeptide fragment. The determination of the nucleotide sequence of a known nucleic acid does not make the nucleic acid patentable over the prior art because the sequence is an inherent characteristic possessed by the nucleic acid of Nobori et al. Therefore, for these reasons the rejection is maintained.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39-42,45-66,74-75,77-83,88-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nobori et al. For the reasons given in the previous action.

Response to Arguments

The response argues that since physical map of the cDNA containing the 3' end of the MTAP gene shown in the Nobori et al. (1994) references is incorrect, the ordinary artisan would have been lead to look in the wrong place for a polynucleotide comprising SEQ ID NO 1.The response alleges, therefore, that Nobori et al. teach away from the present invention. The response asserts that the MTAP probe of Nobori et al. only meets an obvious to try standard and does not meet the prima facie obvious test. The response argues that since Nobori et al. Did not teach the nucleotide sequence of the full length MTAP gene, the reference does not teach that they were in possession of the MTAP gene prior to the present invention. The response cites *in re Eli Lilly & Co.* and *in re Deuel* to show that Nobori is insufficient as a reference.

All of the arguments have been thoroughly reviewed but are deemed non-persuasive for the following reasons. In general Applicant's arguments are directed to an embodiment to which the claims are not limited. There is no argument that Nobori et al. Does not teach the complete MTAP gene of SEQ ID no 1 encoding the a polypeptide of SEQ ID NO 2. However, the claims are not limited to such polynucleotides. Instead the claims 39-53 encompass a genus of polynucleotides which encode SEQ ID NO 2. That is, the polynucleotide can have a large

number of different sequences as long as the encoded amino acid sequence is SEQ ID NO 2. Claims 54-76 are more broadly drawn to a very large genus of polynucleotides which do not have encode the full length MTAP gene and which can vary in sequence as long as they hybridize SEQ ID NO 1. Consequently, while the examiner is in agreement with Applicant over the non-obviousness of a polynucleotide consisting of SEQ ID NO 1, the probe of Nobori et al. would have been expected by the ordinary artisan to detect the gene which it encodes, namely an MTAP coding sequence because Nobori et al. Specifically identified the fragments as the 3' end of the MTAP gene. The fact that the map of Nobori et al. Was incorrect would not have had any effect on the ability of the 2 kb HinDIII fragment to function as a probe in a hybridization assay on a cDNA library to have detected complementary clones. Chromosome walking is not the only method used to isolate a gene sequence and actually since Nobori et al. Already were in possession of the 3' end of the MTAP gene, the ordinary artisan would have seen that the easiest and quickest way to obtain the remainder of the gene would be to screen the cDNA library for overlapping clones.

Claims 84-87 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nobori et al. for the reasons of record.

Response to Arguments

The response traverses the rejection on the following grounds. Again the response argues that Nobori et al. Does not teach the nucleotide sequence of MTAP gene. And only teaches a 3' fragment of the MTAP gene and teaches the wrong map.

All of these arguments have been thoroughly reviewed but are deemed non-persuasive for the following reasons. The claims are drawn to a kit containing a nucleic acid segment of at least 21 bases from SEQ ID NO 1 and a detection reagent, and a restriction enzyme and another 21 bp fragment of SEQ ID NO 1. The fragment of Nobori is the 3' end of the MTAP gene which clearly is a nucleic acid segment of at least 21 bases from SEQ ID NO 1. It is noted that the actual sequence of the fragment of Nobori et al. Was not taught. However, it is acknowledged by applicant and taught by Nobori et al. That the fragment of Nobori is the 3' end of the human MTAP gene and that SEQ ID NO 1 is the full length coding sequence of the human MTAP gene. Consequently, the ordinary artisan would have expected the Nobori et al. fragment to have the same sequence as the 3' end of SEQ ID NO 1. The fact that the map of Nobori et al. Was incorrect would not have had any effect on the ability of the 2 kb HinDIII fragment to function as a probe in a hybridization assay on a cDNA library to have detected complementary clones. Therefore, for these reasons, the rejection is maintained.

NEW GROUNDS OF REJECTION

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54-60,67-76, 88-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The essential feature of the claimed invention is a nucleic acid comprising a gene encoding a methylthioadenosine phosphorylase (MTAP) having at least 10, 20,or 30 contiguous residues from SEQ ID NO 2 or all of SEQ ID NO 2. The specification describes a cDNA sequence which encodes human MTAP which was used to screen a cosmid library for MTAP genomic sequences. The specification teaches that MTAP is composed of 7 exons in 22 kb and teaches the intron/exon boundaries and teaches a HindIII restriction map of the genomic DNA containing MTAP. However, the specification does not describe the 5' and 3' regulatory regions of the MTAP gene and therefore have not fully described an MTAP gene such that it is clear applicants were in possession of the gene. Additionally, the claims encompass mammalian homologs of the human MTAP gene and encoding polynucleotides but the specification has only described a human MTAP encoding sequence of SEQ ID NO 2 (amino acid sequence) and SEQ ID NO 1 (the nucleotide sequence). The specification teaches that the MTAP gene appears to be highly conserved through evolution as show by a Northern blot analysis using the human MTAP cDNA sequence as a probe at low stringency (page 90 and Figure 13) with DNA isolated from several

tumor cell lines. However, the tumor cell lines are human and mouse and it is unclear if any other species are represented by Figure 13. While showing that an MTAP gene with some sequence similarity to SEQ ID NO1 appears to be present in at least one other mammal, this evidence is not sufficient to show that the human MTAP gene or coding sequence is predictably representative of the claimed genus of mammalian MTAP genes and coding sequences because no common structural feature has been described. Consequently, applicants do not appear to have been in possession of the genus of mammalian MTAP genes or coding sequences other than the human MTAP coding sequence of SEQ ID NO 2 or the polynucleotide sequence of SEQ ID NO 2.

Claims 95-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The essential feature of the claimed invention is an association or correlation of homozygous deletions in the MTAP gene and the presence of a cancer. The specification and the prior art teach that the 9p21 region is often deleted in manner tumor cells and consequently, this region has been studied as a target location for tumor suppressor genes. MTAP activity is often absent in these tumor cells and thus MTAP was found to be linked to the genes in this deleted region (Olopade (1995)). The specification and the art do not provide evidence that the absence

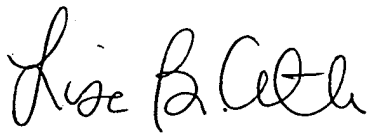
of MTAP alone results in cancer. However, the claims are drawn to a method which identifies a cancer type by determining the deletion pattern within the MTAP gene. Neither the specification nor the art teach that a particular pattern of MTAP deletions identifies a particular type of cancer particular when MTAP has not be identified as a gene which is involved in the tumorigenic characteristic of a gen but has instead been used as a marker for the absence of a region which is suspected to contain other genes, i.e. tumor suppressor gene, that may be important in the development of a cancer. Page 27 of the specification states that homozygous deletions have been found which include all of part of the IFN gene cluster and all or part of the MTAP gene. At page 28, the specification teaches that this is evidence for the presence of a tumor suppressor gene but does not suggest that MTAP is a tumor suppressor gene. The specification contains no description that detection of homozygous deletion in the MTAP gene would allow identification of a cancer cell, and certainly not for a particular cancer type. Consequently, applicants do not appear to have been in possession of the claimed invention at the time of filing.

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Tuesday-Thursday from 7:00 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



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